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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/707,747	01/08/2004	John H Paul	1372.120.PRC	1746

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EXAMINER
THOMAS, DAVID C

ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/707,747	PAUL ET AL.	
	Examiner	Art Unit	
	David C. Thomas	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-21 and 24-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-21 and 24-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 15, 2006 has been entered. Claims 16-18, 20, 21, 25, 27, and 30 (currently amended), and 19, 24, 26, 28, and 29 (original) will be examined on the merits. Claims 31-36 were previously withdrawn and claims 1-15, 22, and 23 have been canceled.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 16-18 are rejected under 35 U.S.C. 103(a) as being anticipated by Yoon et al. (Proc. Natl. Acad. Sci. USA. (2002) 99: 11724-11729) in view of Buck et al. (Biotechniques (1999) 27: 528-536) and further in view of GenBank Accession No. AY119786.

With regard to claim 16, Yoon teaches a method for screening a sample for the presence of *K. brevis,* comprising:

subjecting the sample to amplification using a pair of oligonucleotide primers capable of amplifying a target region of the ribulose 1,5-biphosphate carboxylase-oxygenase large subunit (rbcL) of *K. brevis* (amplification using species-specific primers, p. 11725, column 1, lines 13-24 and Table 2, supporting information); and

assaying the mRNA for the presence of the amplified target region of the ribulose 1,5-biphosphate carboxylase-oxygenase large subunit (rbcL) unique *K. brevis* (PCR products generated from total RNA were sequenced using dye terminators as probes, p. 11725, column 1, lines 20-29; sequences are unique to *K. brevis,* p. 11726, column 1, lines 8-14 and Figure 1A and B and GenBank Accession No. AY119786; BLAST search indicates primers amplify a region unique to *K. brevis*, see BLAST results).

With regard to claim 17, Yoon teaches a method wherein the pair of oligonucleotide primers specifically amplify mRNA of a target region of the ribulose 1,5-biphosphate carboxylase-oxygenase large subunit (rbcL) of *K. brevis* and do not amplify a region of the ribulose 1,5-biphosphate carboxylase-oxygenase large subunit (rbcL) of

K. mikimotoi (detection of *K. brevis* is performed by amplification using species-specific primers, p. 11725, column 1, lines 13-24 and Table 2, supporting information; BLAST search indicates primers amplify a region unique to *K. brevis* and not other *Karenia* species such as *K. mikimotoi*, see BLAST results).

With regard to claim 18, Yoon teaches a method wherein the target region of the ribulose 1,5-biphosphate carboxylase-oxygenase large subunit (rbcL) of *K. brevis* is about 87 to 91 base pairs in length (using primers rbcL64F and R-173 in Table 1, a 155-base pair target would be amplified in rbcL gene region, p. 11724, column 2, lines 29-32, Table 1, supporting information and GenBank Accession No. AY119786).

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoon, which are 100% derived from sequences expressly suggested by the prior art of Yoon as useful for primers for the detection *K. brevis,* and concerning which a biochemist of ordinary skill would attempt to obtain alternate

compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of

extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

5. Claims 19-21, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon et al. (Proc. Natl. Acad. Sci. USA. (2002) 99: 11724-11729) in view of Bowers et al. (Appl. Environ. Microbiol. (2000) 66: 4641-4648) and further in view of Wilson et al. (J. Microbiol. Meth. (1999) 39:59-78) and further in view of Buck et al. (Biotechniques (1999) 27: 528-536) and further in view of GenBank Accession No. AY119786.

Yoon, in view of Buck and GenBank Accession No. AY119786, teaches the limitations of claims 16-18 as discussed above.

With regard to claims 20 and 21, Yoon also teaches a method wherein the pair of oligonucleotide primers consist of SEQ. ID. No. 1 (Table 1, supporting information, GeneBank Accession No. AY119786, positions 729-748) and SEQ. ID. No. 2 (Table 1, supporting information, GeneBank Accession No. AY119786, positions 819-798), wherein SEQ. ID. No. 1 comprises a forward primer (GeneBank Accession No. AY119786, positions 729-748) and SEQ. ID. No. 2 comprises a reverse primer (GeneBank Accession No. AY119786, positions 819-798), to generate a 91-base pair amplicon (from positions 729 to 819 of GeneBank Accession No. AY119786).

With regard to claims 24 and 25, Yoon also teaches a method wherein the amplification process is applied to the sample in the presence of a probe, wherein the probe consists of SEQ. ID. No. 6 (Table 1, supporting information, GeneBank Accession No. AY119786, positions 703-726).

Yoon does not teach a method for screening a sample for the presence of *K. brevis* using a real-time reverse transcriptase polymerase chain reaction or quantitative thermocycling. Yoon also does not teach methods of designing species-specific primer sets to amplify unique regions of the rbcL gene of *K. brevis* including primers consisting of SEQ ID Nos. 1 and 2 and a probe consisting of SEQ ID No. 6.

Bowers teaches a method of specifically detecting harmful algal bloom species including dinoflagellates such as *Pfiesteria* using a real-time polymerase chain reaction (p. 4643, column 1, lines 19-23) and internal probes (p. 4643, column 1, lines 23-30 and p. 4645, column 1, lines 8-14). Bowers demonstrates specific detection of *Pfiesteria* species in the presence of negative control samples including other harmful dinoflagellate species such as *K. brevis* (p. 4645, column 1, line 37 to column 2, line 13 and Table 1, *Gymnodinium breve=K. brevis*).

Bowers does not teach the detection of *K. brevis* sequences by the real time polymerase chain reaction using at least one specific primer and a probe. Bowers also does not teach methods of designing species-specific primer sets to amplify unique regions of the rbcL gene of *K. brevis,* including primers consisting of SEQ ID Nos. 1 and 2 and a probe consisting of SEQ ID No. 6.

Wilson teaches methods of designing species-specific primer sets by sequence alignment techniques in order to amplify unique regions of the 16S rRNA gene for purposes of detecting different microorganisms in water samples (p. 60, column 2, lines 5-16, p. 62, column 1, lines 35-40 and Figure 1).

Wilson does not teach a method for screening a sample for the presence of *K. brevis* using a real-time reverse transcriptase polymerase chain reaction or quantitative thermocycling. Wilson also does not teach methods of designing species-specific primer and probe sets to amplify unique regions of the rbcL gene of *K. brevis,* including primers consisting of SEQ ID Nos. 1 and 2 and a probe consisting of SEQ ID No. 6.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Yoon, Bowers and Wilson since Yoon teaches the detection of a sequence specific to *K. brevis* in the rbcL gene using a reverse-transcriptase polymerase chain reaction method, while Bowers describes a real-time polymerase chain reaction using an internal fluorescent probe to detect harmful dinoflagellates in a rapid, homogeneous assay, and Wilson teaches methods to design species-specific primers in order to detect single species in samples containing many different related or unrelated species. Thus, an ordinary practitioner would have been motivated to combine these methods to provide a rapid test for harmful algal bloom species that results in an added level of specificity compared with assays based on traditional PCR methodology. The use of a high through-put real-time PCR assay greatly improves upon other traditional methods of processing large numbers of environmental water samples such as scanning electron microscopy which

are very labor-intensive, and also provides a method that is more easily adapted for field-based testing. Furthermore, the methods of Wilson provide a highly powerful approach to species-specific detection using competitive PCR since unique primer sets that can be designed for multiplexed assays (Wilson, p. 74, column 2, lines 3-8, and also those containing internal controls by using universal primers sets in conserved regions of the target gene (Wilson, p. 72, column 2, line 43 to p. 73, column 1, line 8).

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious.

Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoon, which are 100% derived from sequences expressly suggested by the prior art of Yoon as useful for primers for the detection *K. brevis,* and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence

as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all

possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

6. Claims 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon et al. (Proc. Natl. Acad. Sci. USA. (2002) 99: 11724-11729) in view of Leone et al. (Nucleic Acids Res. (1998) 26: 2150-2155) and further in view of Wilson et al. (J. Microbiol. Meth. (1999) 39:59-78) and further in view of Buck et al (Biotechniques (1999) 27: 528-536) and further in view of GenBank Accession No. AY119786.

Yoon, in view of Buck and GenBank Accession No. AY119786, teaches the limitations of claims 16-18 as discussed above.

With regard to claims 27 and 30, Yoon also teaches a method wherein the pair of oligonucleotide primers specific to a target region of the ribulose 1,5-biphosphate carboxylase-oxygenase large subunit (rbcL) of *K. brevis* consist of SEQ. ID. NO. 4 (Table 1, supporting information, Gene Bank Accession No. AY119786, positions 733-751) and SEQ. ID. No. 5 (Table 1, supporting information, Gene Bank Accession No. AY119786, positions 819-798, representing the 22 3-prime most bases of this NASBA primer complementary to the target; the remaining portion SEQ ID No. 5 serves as a transcription initiation sequence, see Leone, Figure 6), to generate an 87-base pair amplicon (from positions 733 to 819 of GeneBank Accession No. AY119786).

With regard to claim 29, Yoon also teaches a method wherein the probe comprises a nucleotide sequence consisting of SEQ. ID. No. 3 (Table 1, supporting information, Gene Bank Accession No. AY119786, positions 758-775).

Yoon does not teach a method of screening a sample for the presence of *K. brevis* using nucleic acid sequence based amplification in the presence of a probe, including primers consisting of SEQ ID Nos. 4 and 5 and a probe consisting of SEQ ID No. 3.

With regard to claims 26-30, Leone teaches a method of homogeneous real-time detection of RNA using nucleic acid sequence based amplification and molecular beacon probes (p. 2151, column 1, lines 6-15 and line 42 to column 2, line 12).

Leone does not teach a method of detection of *K. brevis* sequences by nucleic acid sequence based amplification using at least one specific primer and a probe including primers consisting of SEQ ID Nos. 4 and 5 and a probe consisting of SEQ ID No. 3.

Wilson teaches methods of designing species-specific primer sets by sequence alignment techniques in order to amplify unique regions of the 16S rRNA gene for purposes of detecting different microorganisms in water samples (p. 60, column 2, lines 5-16, p. 62, column 1, lines 35-40 and Figure 1).

Wilson does not teach a method for screening a sample for the presence of *K. brevis* using a real-time reverse transcriptase polymerase chain reaction or quantitative thermocycling. Wilson also does not teach methods of designing species-specific primer and probe sets to amplify unique regions of the rbcL gene of *K. brevis,* including primers consisting of SEQ ID Nos. 4 and 5 and a probe consisting of SEQ ID No. 3.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Yoon, Leone and Wilson

since Yoon teaches the detection of a sequence specific to *K. brevis* in the rbcL gene using a reverse-transcriptase polymerase chain reaction method, while Leone teaches an alternative method of DNA detection, nucleic acid sequence-based amplification (NASBA), that can also be adapted to a real-time format, and thus is very suitable for detection of dinoflagellate species such as *K. brevis,* and Wilson teaches methods to design species-specific primers in order to detect single species in samples containing many different related or unrelated species. Thus, an ordinary practitioner would have been motivated to combine these methods to provide a rapid test for harmful algal bloom species that results in an added level of specificity compared with amplification assays based on traditional non-fluorescence methodologies. Because NASBA is an isothermal process that doesn't require heavy equipment such as thermocyclers, when combined with molecular beacon probes, this method is suitable for high through-put sample analysis and the development of automated workstations, and is also easily adapted for field-based testing. Because the method is ideally suited for amplifying RNA analytes using one reaction mixture, the application range is expanded beyond genomic targets to gene expression targets such as the mRNA product of the rbcL gene of *K. brevis.* Furthermore, the methods of Wilson provide a highly powerful approach to species-specific detection since unique primer sets that can be designed for multiplexed assays (Wilson, p. 74, column 2, lines 3-8, and also those containing internal controls by using universal primers sets in conserved regions of the target gene (Wilson, p. 72, column 2, line 43 to p. 73, column 1, line 8).

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious.

Regarding structural or functional homologs, however, the Court stated,

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Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoon, which are 100% derived from sequences expressly suggested by the prior art of Yoon as useful for primers for the detection *K. brevis,* and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Response to Arguments

7. Applicant's arguments filed December 15, 2006 have been fully considered but they are not persuasive.

The applicant argues that Yoon does not teach, describe or suggest a sequence unique to *K. brevis* and does not teach or suggest all of the limitations of the claims as amended. Yoon clearly states that species-specific primers were used in the PCR amplification of some sequences such as the *psaA* gene for some algal species, (p. 11725, column 1, lines 16-18), though general primers were used in other cases and also for the rbcL gene (Table 2). However, upon further analysis of the sequence amplified by the rbcL gene primers taught by Yoon (Table 2), the amplified target region sequence is unique to *K. brevis* based on a BLAST search of the 158-basepair amplicon (see BLAST search results) and does not share extensive homology with *K. mikimotoi*. Therefore, Yoon teaches species-specific detection of *K. brevis,* as is required to meet the limitation of claim 16 that a unique target region is amplified. However, even if the primers taught by Yoon were to amplify a region of the rbcL gene of a related species such as *K. mikimotoi*, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to design other species-specific primers based on the known sequence of the *K. brevis rbcL* gene (Gene Bank Accession No. AY119786) for the purposes of species-specific screening of samples for detection of this organism. To this end, Wilson teaches methods of primer design for species-specific detection of microorganisms in water samples (p. 60, column 2, lines 5-16, p. 62, column 1, lines 35-40 and Figure 1). This method utilizes software that aligns sequences of related species to design primers that are specific to only one

species in a sample containing large numbers of microorganisms and therefore is directly applicable to design of primers to amplify organisms such as *K. brevis* in the presence of related organisms such as *K. mikimotoi* or other algae species.

Applicant also argues that the GenBank sequence AY119786 that is homologous to the SEQ. ID. numbers represents only a portion of the rbcL gene and that there is no teaching in Yoon as to what portion of the sequence is unique to *K. brevis*. While Yoon does not directly define the unique portions of the rcbL gene unique to *K. brevis*, the primer binding sequences would be expected to be unique since the primers of the invention are an exact match of the GenBank sequence. It would be expected that the sequences spanned by the amplification primers would also be unique to *K. brevis*, though flanking sequences may not necessarily be unique. It is not necessary to define portions of the gene not required for detection. Finally, it is irrelevant what form of the gene is represented in the deposit, since at least one unique portion of the gene is included to allow design of species-specific primers and probes for detection of the target sequences in question. Therefore, the 103 rejections based on the Yoon reference in view of GenBank Accession No. AY119786 and further in view of either Bowers, Wilson and Buck or Leone, Wilson and Buck are maintained.

In view of the amended claims, the 112, second paragraph rejection of claim 16 has been withdrawn.

Conclusion

8. Claims 16-21 and 24-30 are rejected. No claims are allowable.

Correspondence

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David C. Thomas 1/5/07
David C. Thomas
Patent Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER
1/5/07